EXHIBIT 6

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SIDLEY AUSTIN LLP
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EXAMINER	
ART UNIT	PAPER NUMBER

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action in Ex Parte Reexamination	Control No. 90/007,542 (90/007,854)	Patent Under Reexamination 6331415	
	Examiner Bennett Celsa	Art Unit 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a☒ Responsive to the communication(s) filed on *30 October 2006*. b☒ This action is made FINAL.
c☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire *2* month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-36* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1-36* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____.
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

Reexamination: Final Office Action

Reexamination of US Patent No. 6,331,415 (Cabilly 2 patent).

Status of the Claims

Claims 1-36 are pending and under reexamination. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Procedural Posture:

Merger of 3rd Partly Requests 90/007,542 and 90/007,859

	i. 90/007542 ('7542 Proceeding):	ii. 90/007859 ('7859 Proceeding)
Reexamination request filed:	5/13/05	12/23/05
Reexamination ordered:	7/7/05.	1/23/06
Patent Owner Statement:	none	none
First Office Action mailed:	9/13/05	N/A
Patent Owner Response dated	1/25/05	N/A
'7542 AND '7859 merged:	6/6/06	

Following the merger of the 90/007,542 and 90/007,859 proceedings, the First Office Action dated September 13, 2005 in the '7542 proceeding was withdrawn in light of the Non-Final Office Action dated August 16, 2006.

Patentee's November 25, 2005 response (with Declarations) and the November 30, 2006 response (with Declarations) to the September 13, 2005 and subsequent August 16 2006 office actions, respectively in the 90/007,542 proceeding are considered in this office action.

Additionally, the submitted December 14, 2006 and January 16, 2007 information disclosure statement have been considered in this office action.

Information Disclosure Statement (IDS)

Examiner-initialed copies of the December 14, 2006 IDS (four pages) and the

January 16, 2007 IDS (thirty pages) submitted under Rule 1.97(c), (requiring 1.17(p) fees), accompany this office action. The newly submitted Moore 5,840,545 Patent reference presented in the Dec. 14th IDS necessitated the making of the new grounds of rejection found in this office action.

There is a substantial new question of patentability raised by the Moore 5,840,545 patent. The Moore patent was cited by the Examiner in an anticipation rejection in a related co-pending application (U.S.S.N. 08/422,187) but is now being viewed in a new light since the claims addressed in 08/422,187 were drawn to different subject matter (e.g. process for producing altered antibody heavy or light chain or fragments thereof).

Priority

The 6,331,425 (Cabilly 2) patent undergoing reexamination issued on December 18, 2001 from application 07/205,419 (filed 6/10/88) which was a continuation of 06/483,457 (filed 4/8/83) now 4,816,567 (Cabilly 1) patent.

Cumulative Prior Art :

The 1982 Valle and Deacon references are cumulative in their teaching of microinjection of mRNA encoding light and heavy immunoglobulin chains into Xenopus oocyte cells to produce secreted active antibody. Accordingly, only the Deacon reference was utilized in the obviousness double patenting rejection(s) recited below.

Additionally, the Oi and Ochi references are cumulative in their teaching of restoring hybridoma cell antibody expression by vector transformation with a light chain

gene. Accordingly, only the Ochi reference was utilized in the obviousness double patenting rejection(s) recited below.

Further, the Moore et al. 4,642,334 patent (*claiming functional single chain antibodies*) is deemed cumulative to the child Moore et al. 5,840,545 patent reference cited below (drawn to the methods and vectors used in making single chain antibodies).

Withdrawn Objection (s) and/or Rejection (s):

The following obviousness double patenting rejections raised in the August 16, 2006 office action are hereby withdrawn for the following reasons:

1. Claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 of U.S. Pat. No. 6,331,415 (Cabilly 2) rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (3/89: Cabilly 1) (wherein "or" is being *interpreted as "and"* in light of the Cabilly 1 patent prosecution history).

2. Claims 1-36 of U.S. Pat. No. 6,331,415 (Cabilly 2) are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) as applied to claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 (wherein "or" is being interpreted as "and" in light of the Cabilly 1 patent prosecution history) and further in view of Axel et al U.S. Pat. No. 4,399,216 (8183), Rice et al. PNAS USA 79(12182):7862-7865, Kaplan et al. EP 004722 (1182), Builder et aL U.S. Pat. No. 4,511,502 (issued 4/85), Accolla et al. PNAS USA 77(1): 563-566 Dallas (WO 82/03088), Deacon (Biochemical. Society Transactions, 4 (1976):818-820), 1981 Valle (Nature, 291 (May '81) pages 338-340; and Ochi(Nature, 302(3124183) pages 340-342).

To the extent the above obviousness double patenting rejections were predicated on claim interpretation that "or" is equivalent to "and", patentee's arguments and evidence regarding claim interpretation of "or" (as meaning "or") in the parent Cabilly 1 patent application was found persuasive.

In response to the above double patenting rejections, patentee argued (See October 30, 2006 patentee response particularly at pages 4-5 top and pages 10-20), that the prosecution history of the parent application (Cabilly 1) supports an

interpretation that "or" has its ordinary meaning ("or" is "or") and not "and/or". Relevant in this regard was the prosecution history of the parent Cabilly 1 application described on pages 11-14 of the owner's response to an Examiner indefinite rejection which demonstrated that "or" was being defined by the patentee and the Examiner as having its conventional alternative meaning. Accordingly, the above obviousness double patenting rejections, to the extent that they were predicated on "or" as being interpreted to include "and", have been overcome.

3. Claims 1-36 of U.S. Pat. No. 6,331,415 (Cabilly 2) are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) as applied to claims 1-4, 11, 13, 15-18, 21, 23-25 and 33 (wherein "or" is being interpreted as "and" in light of the Cabilly 1 patent prosecution history) and further in view of Axel et al U.S. Pat. No. 4,399,216 (8183), Rice et al. PNAS USA 79(12182):7862-7865, Kaplan et al. EP 004722 (1182), Builder et aL U.S. Pat. No. 4,511,502 (issued 4/85), Accolla et al. PNAS USA 77(1): 563-566 Dallas (WO 82/03088), Deacon (Biochemical. Society Transactions, 4 (1976):818-820), 1981 Valle (Nature, 291 (May '81) pages 338-340; and Ochi(Nature, 302(3124183) pages 340-342).

The obviousness double patenting rejection cited above (predicated on "or" as having its ordinary meaning) in which the Cabilly 1 patent was combined with the Axel, Rice et al., Kaplan et al., Builder et al., Acolla et al., Dallas, Deacon, Valle (1981) and Ochi references is withdrawn in light of a newly presented modified rejection which further includes the newly submitted Moore et al. U.S. Pat. No. 5,840,545.

The Instant 6,331,415 (Cabilly 2) Patented Invention Undergoing Reexamination

The following patent claim methods and compositions are representative:

i. METHODS:

1. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell comprising:

(i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain, and

(ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell. See Claim 1.

33. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell comprising:
independently expressing a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a. second DNA sequence encoding at least the variable domain of the immunoglobulin light chain so that said immunoglobulin heavy and light chains are produced as separate molecules in said single host cell transformed with said first and second DNA sequences.

21. A method comprising:

a) preparing a DNA sequence consisting essentially of DNA encoding an immunoglobulin consisting of an immunoglobulin heavy chain and light chain or Fab region, said immunoglobulin having specificity for a particular known antigen;

b) inserting the DNA sequence of step a) into a replicable expression vector operably linked to a suitable promoter;

c) transforming a prokaryotic or eukaryotic microbial host cell culture with the vector of step b);

d) culturing the host cell; and
e) recovering the immunoglobulin from the host cell culture, said immunoglobulin being capable of binding to a known antigen.

ii. COMPOSITIONS:

15. A vector comprising a DNA encoding at least a (first) variable immunoglobulin heavy chain domain and a second DNA sequence encoding at least a variable immunoglobulin light chain domain wherein the 1st and 2nd DNA sequences are located at different insertion sites in the vector.

18. A transformed host cell comprising at least two vectors in which one vector comprises a variable immunoglobulin heavy chain domain and a second vector comprises a variable immunoglobulin light chain domain.

32. The insoluble particles of heavy and light chains or Fab region produced by the method of claim 21 in which the heavy and light chains or Fab regions are deposited within the cells (e.g. claim 27).

The Reference US Pat. No. 4,816,567 Cabilly 1 Patent Claims:

a. The Cabilly I ('567 Patent) Claims

Independent claims 1, 3, 5, and 7 of the '567 patent read as follows;

1. A method comprising
a) preparing a DNA sequence encoding a chimeric immununoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mnmmalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species;
b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell;
c) transforming the host cell with the vector of (b);
d) culturing the host cell; and
e) recovering the chimeric heavy or light chain from the host cell culture.

3. A composition comprising a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen having a constant region homologous to a corresponding constant region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

5. A replicable expression vector comprising DNA operably linked to a promoter compatible with a suitable host cell, said DNA encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen and having a constant region homologous to a corresponding region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

7. Recombinant host cells transformed with the vector of claim 5.

Claims 2, 4 and 6 (dependent on claims 1, 3 and 5, respectively) recite that the first mammalian species (i.e. the source of the constant region) is human.

Cabilly 1 ('567 Patent) and Cabilly 2 ('415 Patent) Claim Interpretation

Antibodies are proteins which generally refer to tetramers or aggregates thereof having specific immunoreactive activity comprising light and heavy chains in a "Y" configuration (having variable branch and constant stem regions), with or without covalent linkage. '567 patent col. 6, lines 14-18.

Similarly, an "immunoglobulin" generally comprises two heavy and two light chains "but may have specific immunoreactive activity (i.e. an "antibody") or lack such specific immunoreactive activity (i.e. "non-specific immunoglobulin" or "NSI"). See Cabilly I patent col. 6, lines 18-20; and Cabilly 2 patent Fig. 1.

The phrase "chimeric immunoglobulin heavy or light chain" refers to a species of immunoglobulin heavy or light chain in which the constant region is homologous to the constant region of an antibody of a first mammalian species and the variable region is homologous to the variable region of an antibody derived from a second, different mammalian species. See claim 1 and 3 definition; '567 patent col. 6, lines 48-59.

The phrase "replicable expression vector (comprising DNA) operably linked to a suitable promoter compatible with a host cell" of Cabilly 1 claims 1 and 5 is discussed in the '567 patent specification. An "expression vector" includes:

> ... vectors which are capable of expressing DNA sequences contained therein, i.e., the coding sequences are operably linked to other sequences capable of effecting their expression. It is implied, although not always explicitly stated, that these expression vectors must be replicable in the host organisms . . . .
>
> '567 patent, col. 8, 11. 21-27.

"Host cells," as recited in Cabilly 1 claims 1 and 7, include prokaryotic or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See '567 patent, col. 8, line 46 to col. 10, 1ines 13-30, 57

The final step of the Cabilly 1 claim 1 process calls for "recovering the chimeric heavy or light chain from the host cell culture": "[t]he protein thus produced is then recovered from the cell culture by methods known in the art, but the choice of which is necessarily dependent on the form in which the protein is expressed. " '567 patent, col. 13, lines 3-6.

The recombinant procedures used to obtain the DNA sequences, prepare vectors, transform cells, culture cells, and recover the immunoglobulins are the same, whether for recombinant immunoglobulins that mimic naturally occurring ones or for altered recombinant immunoglobulins, such as chimeric antibodies. See e.g., '567 patent, col. 15; lines 59 to col. 16, line 15; and col. 28, lines 44-47.

New Rejection(s)

Claim Rejections - 35 USC § 102

1. Claims 1-7, 9-10, 14-18 and 21, 23-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Moore et al. U.S. Pat. No. 5,840,545 (Nov. 24, 1998: effective filing date of March 15, 1982 of date of 06/358,414).

Moore et al. disclose and claim a hybrid DNA strategy for the preparation of specific binding polypeptides comprised of two different polypeptide chains, which together assume a conformation having high binding affinity to a predetermined ligand

or haptenic site thereof (see e.g. Moore '545, col. 2, lines 39-52). One or both of the different polypeptide chains derived from the variable region of the light and heavy chains of an immunoglobulin may be used to provide specific binding analogous to the binding site of an immunoglobulin, with the composition being referred to as an "rFv" and with the portions corresponding to L-rFv (variable light region of an antibody) and H-rFv (variable heavy region of an antibody), thus forming a functioning single chain antibody (compare to instant patent "Fab proteins" or "univalent antibodies": Cabilly '415 patent col. 5, lines 17-28).

For example the Moore Patent claims:

> 1. A host cell which expresses a recombinant double-chain antibody fragment (rFv) comprising two polypeptide chains having substantially the same amino acid sequence of at least a portion of the variable region, without constant region amino acids, of a mammalian immunoglobulin, the immunoglobulin having binding specificity to a predetermined ligand, wherein the polypeptide chains are prepared by expression of a DNA sequence coding for the variable region, said expression occurring in the absence of expression of a DNA sequence coding for a natively associated constant region, and wherein the two polypeptide chains combine to form the rFv which has a high affinity and specificity for the predetermined ligand.
>
> and
>
> 2. A method of synthesizing an rFv fragment comprising:
>
> (1) cloning first and second DNA molecules respectively encoding heavy and light chains from a hybridoma producing an antibody to a predetermined ligand;
>
> (2) tailoring the cloned DNA molecules to express fragments comprising 95-125 amino acids of the heavy and light chain variable regions, without constant regions, in a host cell;
>
> (3) inserting the tailored DNA molecules into an expression vector in proper relationship with transcriptional and translational regulatory signals in the vector;

(4) transforming the host cell with the expression vector and growing the host cell, whereby the light and heavy variable region polypeptides are expressed and associate to form an rFv having substantially the same binding specificity for the predetermined ligand as the antibody from the hybridoma.

Accordingly, the Moore patent discloses and claims a method of making an "immunologically functional immunoglobulin fragment" (as in instant claims 1, 21 and 33 and dependent claims thereon) comprising independently expressing in a host variable heavy and light chain domains (e.g. rFV including heavy chain gamma and light chain kappa as in instant claims 23-25: see col. 1, lines 33-42; col. 3, lines 59-63; col. 17, lines 4-8) lacking constant regions, and a "host cell" transformed with a single genetic construct (e.g. a vector or plasmid, including pBR322; see e.g. Moore at col. 5, lines 32-35: wide variety of vectors may be employed for amplification or expression; and col. 7, lines 39-50 exemplifying vectors including pBR322) or two separate constructs comprising DNA (e.g. ds cDNA derived from a monoclonal produced by a hybridoma as in instant claim 14: see Moore patent claim 2) encoding variable light and heavy chains (e.g. see Moore patent claim 1; col. 10, lines 1-5; col. 23, lines 35-45 (pBR322); and col. 24, lines 50-60 (pGM1L and pGM1H); col. 11, lines 5-12), thus anticipating instant claims *1-5, 14-18, 21, 23-25 and 33*.

The Moore patent further teaches "appropriate host cells" including non-secreting gram negative bacteria (e.g. E. Coli: which form intracellular rFV precipitates requiring lyses, denaturant solubilization and refolding as in instant claims 6-7, 10, 26-28, 30 and 32: see Moore at col. 10; bottom of col. 24-col. 25, line 27) as well as secreting hosts (e.g. S. cerevisiae or yeast as in instant claims 6-7, 9, 29: see e.g. Moore col. 5, lines

47-52) from which functioning rFV is recovered (as in instant claim 31). See also Moore patent claims; col. 3; col. 10, lines 8-30 and 39-55; col. 11 and examples). Moore additionally teaches the diagnostic and therapeutic use of their isolate rFV antibodies by labeling the variable light and/or heavy chains with diagnostic labels (e.g. fluorescers as a "label") or "hazardous labels" (e.g. radioisotopes and toxins as a "drug") for therapeutic use in mammalian subjects (as in instant claims 34-36). See Moore Abstract; col. 3; and columns 25-26. Thus Moore further *anticipates instant claims 6-7, 9-10, 26-32 and 34-36.*

2. Claims 1-7, 9-10, 14-21 and 23-36 rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al. U.S. Pat. No. 5,840,545 as applied above against claims 1-7, 9-10, 14-18, 21 and 23-36 alone, or if necessary further in view of Axel et al. U. S. Pat. No. 4,399,216 (Aug. 1983: filed Feb. 25, 1980) as applied against instant claims 19-20 (mammalian host cell).

The Moore patent anticipating teaching discussed *supra* against instant claims 1-7, 9-10, 14-18, 21 and 23-36 is herein incorporated in its entirety.

The Moore patent reference differs from instant claims 19-20 by failing to specifically teach expressing their single chain antibody (comprising variable chain light and heavy fragments) in a mammalian host cell.

However, it is noted that the Moore patented invention is *broadly applicable* to the use of any "host cell", including secreting eukaryotic (e.g. yeast) and non-secreting bacterial (e.g. E.coli) host cells for making single-chain antibodies. Additionally, the Moore patent specifically teaches utilizing mammalian derived gene sequences from

hybridomas for obtaining single chain antibody mammalian mimics for therapeutic use in mammals. See Moore at col. 3, lines 59-col.4, lines 30; col. 25-26.

Thus, the Moore patent reference would render the selection of a mammalian host cell from a small number of alternative host cells (e.g. yeast or bacteria) for antibody expression prima fascie obvious to one of ordinary skill in the art at the time of the instant invention, especially in view of the Moore teaching toward the making of mammalian antibody mimics for use in mammalian therapy.

Additionally, in this regard, the Axel reference teaches the advantageous use of eukaryotic (e.g. mammalian) host cells, compared to bacterial host cells, for the expression of proteinaceous materials, including antibodies. The advantages of using a mammalian host cells include the ability to use unaltered genes coding for protein precursors which are converted by the eukaryotic cell to the desired protein (Axel at col. 36-41), the ability to produce glycosylated eukaryotic proteins (Axel at col. 3, lines 3-7) and the absence of bacterial endotoxins (Axel, col. 3, lines 8-12). The Axel patent further teaches a process for inserting DNA into eukaryotic cells, particularly DNA which includes a gene or genes (i.e. DNA 1) coding for desired proteinaceious materials for which no selective criterior exists by including in the genetic construct DNA encoding a reporter protein (i.e. DNA II). See Axel Abstract; and patent claims, especially claims 1,2,7, 22-24, 26-32, 37, 51-55 and 60.

Accordingly, the Axel reference provides further motivation to one of ordinary skill in the art to utilize mammalian host cells as the "appropriate host cell" in the Moore method of producing single chain antibodies.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the instant invention to utilize a mammalian host cell (as in instant claims 19-20) in the Moore method in light of the Axel reference teaching of the advantageous use thereof in methods of making proteins, including antibodies.

3. Claims 1-7, 9-10, 14-18 and 21-36 rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al. U.S. Pat. No. 5,840,545 as applied above against claims 1-7, 9-10, 14-18 and 21, 23-36 and in view of *Accolla et al.* PNAS USA 77(1) 563-566 (January 1980) as applied against instant claim 22 (anti-CEA antibody).

The Moore patent anticipating teaching discussed *supra* against instant claims 1-7, 9-10, 14-18, 21 and 23-36 is herein incorporated in its entirety.

The Moore patent reference differs from instant claim 22 by failing to specifically teach making a single-chain antibody to CEA (i.e. carcinoembryonic antigen).

However, the *Moore* patented method is broadly useful for making (using hybridoma technology) single-chain antibodies "for any ligand", with exemplification of dinitrophenyl (example 1), K-chain (light chain) of MOPC41 and the heavy chain of myeloma S107 which represents a tumor ligand (see col. 11, lines 30-37; Example 1; col. 17, lines 1-10 *et seq*; and patent claims 1-2). Moore additionally teaches the diagnostic and therapeutic use of their rFV antibodies by labeling the variable light and/or heavy chains with diagnostic labels (e.g. fluorescent "label") or "hazardous labels" (e.g. radioisotopes and toxins as a "drug") for therapeutic use in mammalian subjects (as in instant claims 34-36). See Moore Abstract; col. 3 and columns 25-26. Moore's use of single-chain antibodies lacking an immunogenic immunoglobulin

constant region makes Moore's single-chain antibodies more advantageous for *in vivo* diagnosis or therapeutic use. See Moore at col. 1, lines 64-col. 2, lines 8.

Carcinoembryonic antigen (CEA) is a glycoprotein antigen present exclusively in adenocarcinoma of the human digestive tract and in digestive fetuses of 2-6 month gestation (see *Accola* at page 563, left column). *Accola* et al. describe making (using hybridoma technology) labeled monoclonal antibodies to CEA for *in vitro* and *in vivo* diagnostic use (e.g. antigen identification in human tissues and body fluids). See Abstract.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the instant invention to utilize the Moore method to make less immunogenic single chain antibodies to CEA for their recognized use in *in vivo* diagnostics or therapeutics against human adenocarcinoma as taught by Accola.

OBVIOUSNESS DOUBLE PATENTING

4. Claims 1-7, 9-11, 13-18, 21 and 23-36 of U.S. Pat. No. 6,331,415 (Cabilly 2) are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) and Moore et al. U.S. Pat. No. 5,840,545 (Nov. 24, 1998: effectively filed March 15, 1982).

The Reference Cabilly 1 Patent Claims:

The Cabilly 1 patented invention is drawn to:

Claim 1: A method comprising

a) preparing a DNA sequence encoding a chimeric immununoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species;

b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell;

c) transforming the host cell with the vector of (b);

d) culturing the host cell; and

e) recovering the chimeric heavy or light chain from the host cell culture.

Claim 3: A composition comprising a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen having a constant region homologous to a corresponding constant region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

Claim 5: A replicable expression vector comprising DNA operably linked to a promoter compatible with a suitable host cell, said DNA encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen and having a constant region homologous to a corresponding region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

Claim 7: Recombinant host cells transformed with the vector of claim 5.

Claims 2, 4 and 6 (dependent on claims 1, 3 and 5, respectively) recite that the first mammalian species (i.e. the source of the constant region) is human (aka: humanized chimeric antibodies).

In the reference Cabilly 1 disclosure, "immunoglobulins" are defined as being comprised of light (kappa or lambda) and heavy chains (gamma, mu, alpha, delta or epsilon), which, if assembled possess "specific immunoreactive activity", and are labeled "antibodies". See Cabilly 1 at col. 3, lines 15-42; col. 6, lines 14-24.

The phrase "chimeric immunoglobulin heavy or light chain" refers to a species of immunoglobulin heavy or light chain in which the constant region is homologous to the constant region of an antibody of a first mammalian species and the variable region is homologous to the variable region of an antibody derived from a second, different mammalian species. See Cabilly 1 patent: col. 6, lines 48-59.

The Cabilly 1 patent includes mammalian chimeric immunoglobulin light and heavy chains which are derived from humans (dependent claims 2 and 4). Mammalian antibody sources are derived *in situ* from mammalian B lymphocytes or from cell culture hybridomas. See Cabilly 1 patent col. 1, lines 38-42.

The Cabilly 1 claimed "(replicable) expression vector" is defined as vectors capable of expressing DNA sequences contained therein which are frequently in the form of plasmids, thus 'plasmid' and 'expression vector' are often used interchangeably. See Cabilly 1 patent col. 8, lines 21-45.

The Cabilly 1 claimed "Host cells" include prokaryotic (most preferably the gram (-) bacteria E. Coli. Strains ATCC: 31446 and 31537) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See Cabilly 1 patent , col. 8, 1ine 46 to col. 10, lines 13-30, 57.

The Cabilly 1 claimed means of successfully "recovering the chimeric heavy or light chain from the host cell culture" (above claim 1 step e) is determined by the type of protein and host organism but utilizes art known techniques including cell lysis of insolubilized particles present in the host (e.g. gram-negative E. Coli) followed by denaturant solubilization unless the host organism normally secretes the protein out of

the cell (e.g. some yeast and gram positive bacteria). See Cabilly 1 patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18.

Both the Cabilly 1 and the instant Cabilly 2 patented inventions include claims directed to the same statutory subject matter, i.e. recombinant processes, vectors and host cells for making immunoglobulins (particularly chimeric immunoglobulins) and immuno- globulin products. The recombinant procedures used to obtain the DNA sequences, prepare vectors, transform cells, culture cells, and recover the immunoglobulins are the same, whether for recombinant immunoglobulins that mimic naturally occurring ones or for altered recombinant immunoglobulins, such as chimeric antibodies. See e.g., '567 patent, col. 15, lines 59 to col. 16, line 15; and col. 28, lines 44-47.

The reference Cabilly 1 patent specification discloses expressing heavy and light chains preferably for immunoglobulin assembly, a utility which is supported by the reference Cabilly 1 claimed antigen specificity of its chains; and thus it is appropriate to construe the reference Cabilly 1 patent claims to suggest production of chimeric immunoglobuins (e.g. antibodies) using recombinant technology, and vectors and host cells for doing so. *Geneva Pharmaceuticals, Inc.*, 349 F.3d at 1385, 68 U.S.P.Q. 2d at 1875.

The instant Cabilly 2 patented generic invention drawn to producing an immunoglobulin (or immunologically active fragment) clearly encompasses the chimeric immunoglobulin species (or immunologically active fragment) as evidenced by instant patent claim13 encompassing a chimeric immunoglobulin.

The reference Cabilly 1 patented invention ***differs*** *from* the instant patent since it fails to claim the co-expression of light and heavy antibody chains in a single host cell.

The instant Cabilly 2 patent expression of a heavy and light chain (using one or two vectors) in a single host cell would nevertheless have been obvious over the Moore reference since the Moore reference provides motivation to co-express (using one or two vectors) the Cabilly 1 patented light and heavy antibody chains in a single host cell.

Moore et al. disclose and claim a hybrid DNA strategy for the preparation of specific binding polypeptides comprised of two different polypeptide chains, which together assume a conformation having high binding affinity to a predetermined ligand or haptenic site thereof (see e.g. Moore '545, col. 2, lines 39-52). One or both of the different polypeptide chains derived from the variable region of the light and heavy chains of an immunoglobulin may be used to provide specific binding analogous to the binding site of an immunoglobulin, with the composition being referred to as an "rFv" and with the portions corresponding to L-rFv (variable light region of an antibody) and H-rFv (variable heavy region of an antibody), thus forming a functioning single chain antibody (compare to instant patent "Fab proteins" or "univalent antibodies": Cabilly '415 patent col. 5, lines 17-28).

For example the Moore Patent claims:

> 1. A host cell which expresses a recombinant double-chain antibody fragment (rFv) comprising two polypeptide chains having substantially the same amino acid sequence of at least a portion of the variable region, without constant region amino acids, of a mammalian immunoglobulin, the immunoglobulin having binding specificity to a predetermined ligand, wherein the polypeptide chains are prepared by expression of a DNA sequence coding for the variable region, said expression occurring in the absence of expression of a DNA sequence coding for a natively associated constant region, and wherein the two polypeptide chains

combine to form the rFv which has a high affinity and specificity for the predetermined ligand.

2. A method of synthesizing an rFv fragment comprising:

(1) cloning first and second DNA molecules respectively encoding heavy and light chains from a hybridoma producing an antibody to a predetermined ligand;

(2) tailoring the cloned DNA molecules to express fragments comprising 95-125 amino acids of the heavy and light chain variable regions, without constant regions, in a host cell;

(3) inserting the tailored DNA molecules into an expression vector in proper relationship with transcriptional and translational regulatory signals in the vector;

(4) transforming the host cell with the expression vector and growing the host cell, whereby the light and heavy variable region polypeptides are expressed and associate to form an rFv having substantially the same binding specificity for the predetermined ligand as the antibody from the hybridoma.

Accordingly, the Moore patent discloses and claims a method of making an "immunologically functional immunoglobulin fragment" (as in instant *claims 1, 21 and 33* and dependent claims thereon) comprising independently expressing in a host cell variable heavy and light chain domains (e.g. rFV including heavy chain gamma and light chain kappa as in instant claims 23-25: see col. 1, lines 33-42; col. 3, lines 59-63; col. 17, lines 4-8) lacking constant regions. Additionally, a "host cell" transformed with a single genetic construct (e.g. including pBR322; see e.g. Moore at col. 5, lines 32-35 and col. 7, lines 39-50) or two separate constructs comprising DNA (e.g. ds cDNA derived from a hybridoma as in instant claim 14: see Moore patent claim 2) encoding variable light and heavy chains [E.g. see Moore patent claim 1; col. 10, lines 1-5; col.

23, lines 35-45 (pBR322); and col. 24, lines 50-60 (pGM1L and pGM1H); col. 11, lines 5-12], thus rendering obvious *claims 1-5, 14-18, 21, 23-25, 33.*

One of ordinary skill in the art would be further motivated to utilize the Moore reference process to make chimeric antibodies (e.g. humanized) as in Cabilly 1 since this represents another solution to the problem faced by Moore of in vivo immunogencity resulting from the use of antibodies comprising constant chains in *in vivo* diagnosis or therapy. Moore's solution was to employ single-chain antibodies lacking constant regions. See Moore at col. 1, lines 64-col. 2, lines 8.

The Moore patent further teaches "appropriate host cells" including non-secreting gram negative bacteria host cells (e.g. *E. Coli*: which form intracellular rFV precipitates requiring lyses, denaturant solubilization and refolding as in instant claims 6-7, 10, 26-28, 30 and 32: see Moore at col. 10; bottom of col. 24-col. 25, line 27) as well as eukaryotic secreting host cells (e.g. *S. cerevisiae* or yeast as in instant claims 6-7, 9, 29: see e.g. Moore col. 5, lines 47-52) from which functioning rFV is recovered (as in instant claim 31). See also Moore patent claims; col. 3; col. 10, lines 8-30 and 39-55; col. 11 and examples). Moore additionally teaches the diagnostic and therapeutic use of their rFV antibodies by labeling the variable light and/or heavy chains with diagnostic labels (e.g. fluorescent "label") or "hazardous labels" (e.g. radioisotopes and toxins as a "drug") for therapeutic use in mammalian subjects (as in instant claims 34-36). See Moore Abstract; col. 3; and columns 25-26. Thus Moore further renders obvious *instant claims 6-7, 9-10, 26-32 and 34-36.*

5. Claims 1-7, 9-11, 13-21 and 23-36 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) and Moore et al. U.S. Pat. No. 5,840,545 as applied above against claims 1-7, 9-11, 13-18, 21 and 23-36 and further in view of Axel et al. U. S. Pat. No. 4,399,216 (Aug. 1983: filed Feb. 25, 1980) as applied against instant claims 19-20 (mammalian host cell).

The combined Cabilly 1 reference patent claims and the Moore patent reference obvious double patenting teaching discussed *supra* against instant claims 1-7, 9-11, 13-18, 21 and 23-36 is herein incorporated in its entirety.

The combined teaching of the Cabilly 1 patent and the Moore patent reference **differs** from instant claims 19-20 by failing to expressly teach antibody expression in a mammalian host cell.

However, it is noted that the Cabilly 1 patented invention (e.g. see patent claim 7 and Cabilly 1 patent col. 8 bottom-col. 9: prokaryote/eukaryote/yeast) is broadly applicable to the use of any host cell, including mammalian host cells. Additionally, Cabilly 1 claims expressing mammalian (e.g. human) sequences in "suitable host cell" which would clearly encompass mammalian, especially human host cells.

Similarly, the Moore patented invention includes secreting eukaryotic host cells (e.g. yeast) and non-secreting bacterial host cells (e.g. *E.coli*) for making single-chain antibodies. Additionally, Moore specifically teaches utilizing mammalian derived gene sequences from hybridomas for obtaining single chain antibody mammalian mimics for therapeutic use in mammals. See Moore at col. 3, lines 59-col.4, lines 30; col. 25-26.

Thus, the Cabilly 1 patent claims and/or the Moore patent reference would render the selection of mammalian host cells, from among a small number of alternative host cells (e.g. yeast or bacteria) for use in antibody expression, *prima facie* obvious to one of ordinary skill in the art at the time of the instant invention.

Additionally, in this regard, the Axel reference further teaches the advantageous use of eukaryotic (e.g. mammalian) host cells, compared to bacterial host cells, for the expression of proteinaceous materials, including antibodies. The advantages of using a mammalian host cell include the ability to use unaltered genes coding for protein precursors which are converted by the eukaryotic cell to the desired protein (Axel at col. 36-41), the ability to produce glycosylated eukaryotic proteins (Axel at col. 3, lines 3-7) and the absence of bacterial endotoxins (Axel at 8-12). The Axel patent further teaches a process for inserting DNA into eukaryotic cells, particularly DNA which includes a gene or genes (i.e. DNA 1) coding for desired proteinaceious materials for which no selective criterior exists by including in the genetic construct DNA encoding a reporter protein (i.e. DNA II). See Axel Abstract; and patent claims, especially claims 1,2, 7, 22-24, 26-32, 37, 51-55 and 60.

Accordingly, the Axel reference provides further motivation to one of ordinary skill in the art to utilize mammalian host cells in the combined Cabilly 1 and Moore method for co-expressing antibody chains in a host cell.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the instant invention to utilize a mammalian host cell (as in instant claims 19-20) in the combined Cabilly 1 and Moore reference patented method in light of the Axel

reference teaching of the advantageous use thereof in methods of making proteins, including antibodies.

6. Claims 1-7, 9-11, 13-18 and 21-36 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) and Moore et al. U.S. Pat. No. 5,840,545 as applied above against claims 1-7, 9-11, 13-18, 21 and 23-36 and in view of *Accolla et al.* PNAS USA 77(1) 563-566 (January 1980) as applied against instant claim 22 (anti-CEA antibody).

The combined Cabilly 1 patent claims and Moore patent reference obvious double patenting teaching discussed *supra* against instant claims 1-7, 9-11, 13-18, 21 and 23-36 is herein incorporated in its entirety.

The combined Cabilly 1 and Moore patent method teaching *differ* from instant claim 22 by failing to specifically teach making an antibody to CEA (carcinoembryonic antigen).

CEA is an antigen within the general scope of a "particular known antigen" of the reference Cabilly patent claim 1. Additionally, the instant Cabilly 2 patentee admits that anti-CEA antibodies are useful for tumor detection and perhaps use in treating tumors that have CEA at their surface. See Cabilly 2 patent, col. 16, lines 31-38 and references cited therein.

Further, the Moore patented method is broadly useful for making (using hybridoma technology) single-chain antibodies "for any ligand", with exemplification of dinitrophenyl (example 1), K-chain (light chain) of MOPC41 and the heavy chain of

myeloma S107 which represents a tumor ligand (see col. 11, lines 30-37 and Example 1; col. 17, lines 1-10 et seq; and patent claims 1-2). Moore additionally teaches the diagnostic and therapeutic use of their isolate rFV antibodies by labeling the variable light and/or heavy chains with diagnostic labels (e.g. fluorescers as a "label") or "hazardous labels" (e.g. radioisotopes and toxins as a "drug") for therapeutic use in mammalian subjects (as in instant claims 34-36). See Moore Abstract; col. 3; and columns 25-26. Moore's single-chain antibodies are useful for *in vivo* diagnosis or therapeutic use. See Moore at col. 1, lines 64-col. 2, lines 8.

Accordingly, both Cabilly 1 and Moore encompass the making of antibodies (e.g. chimeric or single chain) toward tumor antigens, such as CEA.

Accola teaches that carcinoembryonic antigen (CEA) is a glycoprotein antigen present exclusively in adenocarcinoma of the human digestive tract and in digestive fetuses of 2-6 month gestation (see Accola at page 563, left column). *Accola* et al. describe making (using hybridoma technology) labeled monoclonal antibodies to carcinoembryonic antigen (anti-CEA) for *in vitro* and *in vivo* diagnostic use (e.g. antigen identification in human tissues and body fluids). See Abstract.

Thus, It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the instant invention to utilize the combined Cabilly 1 and Moore method to make antibodies directed to CEA for use in *in vivo* diagnostics or therapeutics against human adenocarcinoma as taught by Accola.

7. Claims 1-36 of U.S. Pat. No. 6,331,415 (Cabilly 2) are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) in view of *Axel et al.* U.S. Pat. No. 4,399,216 (8/83), *Rice et al.* PNAS USA 79 (12/82):7862-7865, *Kaplan et al.* EP 004722 (1/82), *Builder et al.* U.S. Pat. No. 4,511,502 (issued 4/85), *Accolla et al.* PNAS USA 77(1): 563-566 (1980), *Dallas* (WO 82/03088), *Deacon* (Biochemical. Society Transactions, 4 (1976):818-820), *1981 Valle* (Nature, 291 (May '81) pages 338-340; and *Ochi* (Nature, 302 (3/24/83) pages 340-342) alone, or if necessary, further in view of *Moore et al.* U.S. Pat. No. 5,840,545 (Nov. 24, 1998: effectively filed March 15, 1982).

The Reference Cabilly 1 Patent Claims:

The Cabilly 1 patented invention is drawn to:

Claim 1. A method comprising

a) preparing a DNA sequence encoding a chimeric immununoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species;
b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell;
c) transforming the host cell with the vector of (b);
d) culturing the host cell; and
e) recovering the chimeric heavy or light chain from the host cell culture.

Claim 3. A composition comprising a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen having a constant region homologous to a corresponding constant region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

Claim 5. A replicable expression vector comprising DNA operably linked to a promoter compatible with a suitable host cell, said DNA encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen and having a constant region homologous to a corresponding region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

Claim 7. Recombinant host cells transformed with the vector of claim 5.

Claims 2, 4 and 6 (dependent on claims 1, 3 and 5, respectively) recite that the first mammalian species (i.e. the source of the constant region) is human.

In the reference Cabilly 1 disclosure, "immunoglobulins" are defined as being comprised of light (kappa or lambda) and heavy chains (gamma, mu, alpha, delta or epsilon), which if when assembled possess "specific immunoreactive activity" are labeled "antibodies". See Cabilly 1 at col. 3, lines 15-42; col. 6, lines 14-24.

The reference Cabilly 1 defines the phrase "chimeric immunoglobulin heavy or light chain" as referring to a species of immunoglobulin heavy or light chain in which the constant region is homologous to the constant region of an antibody of a first mammalian species and the variable region is homologous to the variable region of an antibody derived from a second, different mammalian species. See Cabilly 1 patent: col. 6, lines 48-59.

The reference Cabilly I patent includes mammalian chimeric immunoglobulin light and heavy chains which are derived from humans (dependent claims 2 and 4). Mammalian antibody sources are derived *in situ* from mammalian B lymphocytes or from cell culture hybridomas. See Cabilly 1 patent col. 1, lines 38-42.

The reference Cabilly 1 claimed "(replicable) expression vector" is defined as vectors capable of expressing DNA sequences contained therein which are frequently in

the form of plasmids, thus 'plasmid' and 'expression vector' are often used interchangeably. See Cabilly 1 patent col. 8, lines 21-45.

The reference Cabilly 1 claimed "host cells" include prokaryotic (most preferably the gram (-) bacteria E. Coli. Strains ATCC: 31446 and 31537) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See Cabilly 1 patent , col. 8, 1ine 46 to col. 10, lines 13-30, 57.

The reference Cabilly 1 claimed means of successfully "recovering the chimeric heavy or light chain from the host cell culture" (above claim 1 step e) is determined by the type of protein and host organism but utilizes art known techniques including cell lysis of insolubilized particles present in the host (e.g. gram-negative E. Coli) followed by denaturant solubilization unless the host organism normally secretes the protein out of the cell (e.g. some yeast and gram positive bacteria). See Cabilly 1 patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18.

Both the Cabilly 1 and the instant Cabilly 2 patented inventions include claims directed to the same statutory subject matter: recombinant processes, vectors and host cells for making immunoglobulins (particularly chimeric immunoglobulins) and immunoglobulin products. The recombinant procedures used to obtain the DNA sequences, prepare vectors, transform cells, culture cells, and recover the immunoglobulins are the same, whether for recombinant immunoglobulins that mimic naturally occurring ones or for altered recombinant immunoglobulins, such as chimeric antibodies. See e.g., '567 patent, col. 15, lines 59 to col. 16, line 15; and col. 28, lines 44-47.

The reference Cabilly 1 patent specification discloses expressing heavy and light chains preferably for immunoglobulin assembly, a utility which is supported by the reference Cabilly 1 claimed antigen specificity of its chains; and thus it is appropriate to construe the reference Cabilly 1 patent claims to suggest production of chimeric immunoglobuins (e.g. antibodies) using recombinant technology, and vectors and host cells for doing so. *Geneva Pharmaceuticals, Inc.*, 349 F.3d at 1385, 68 U.S.P.Q. 2d at 1875.

The instant Cabilly 2 patented generic invention drawn to producing an immunoglobulin (or immunologically active fragment) clearly encompasses the chimeric immunoglobulin species (or immunologically active fragment) as evidenced by instant patent claim13 encompassing a chimeric immunoglobulin.

The reference Cabilly 1 patented invention ***differs*** *from* the instant patent since it fails to teach the co-expression of light and heavy antibody chains in a host cell.

i. One of ordinary skill in the art would have been motivated to express, in a single host, light and heavy immunoglobulin chains (using one or two vectors) when viewing the reference Cabilly 1 patented invention in light of the prior art

Axel et al. teach a process for inserting foreign DNA into eukaryotic cells by co-transforming the cells with this foreign DNA and an unlinked DNA that codes for a selectable phenotype not otherwise expressed by the cell (see col. 3, lines 21-27). Axel describes the process as particularly suited for the transformation of DNA into eukaryotic cells for making antibodies (see col. 3, lines 31-36). Axel discloses and claims the expression of antibodies in mammalian host cells as intact (assembled)

proteins. See *Axel:* abstract; col. 5, lines 3-7 and 24-28; patent claims 1, 7, 22-24, 28 and 29.

Rice introduced a recombinant rearranged murine kappa light chain gene construct into an Abelson murine leukemia virus (A-MuLv)-transformed lymphoid cell line which already synthesized y2b heavy chain protein (see page 7862). *Rice* inserted the light chain gene into a plasmid, transfected the cells, and then examined the polypeptides as well as the RNA produced by the cells (see pages 7863-7864 and Figures 2 and 3). Lastly, since the cells were producing both immunoglobulin light and heavy chains, the cells were examined for the ability to assemble the chains into IgG molecules, leading to the observation that "[e]ssentially all of the k chain produced in the K-2 cells appear to be assembled into IgG2b" (see page 7864 and Abstract penultimate sentence). Thus, *Rice* demonstrates the successful expression of both heavy and light chains in a host with subsequent assembly into immunoglobulins.

Kaplan teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains to specific antigens. By using known molecular biology techniques, the mRNA's can be used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins (see page 3, lines 4-9). In addition, *Kaplan* teaches that a variety of host cells (e.g. bacteria and yeast) and plasmids (particularly pBR322) may be used to express recombinant heavy and light chains (see page 10, lines 1-33).

Dallas teaches that two different proteins (in addition to a selectable marker) can be expressed in a single cell and such expression may be accomplished by the use of

two vectors, each containing DNA encoding one of the proteins, or by use of a single vector that contains DNA encoding each of the proteins. (See Example IV, as well as page 8, lines 9-11, which disclose the use of a single vector, and page 9, lines 27-29, which discloses the use of two vectors). More particularly, a plasmid containing a HindIII DNA fragment encoding one protein was subcloned into a separate site of a second plasmid containing a BamHI DNA fragment encoding a second protein to form a single plasmid used for independently expressing both proteins in a single cell. See page 8, lines 11-17 and page 7, lines 29-33.

Thus, the *Axel, Rice* and *Kaplan* references taken in view of the *Dallas* reference teaching would provide motivation to one of ordinary skill in the art at the time the instant invention was made to modify the Cabilly 1 patented invention to transform a single host with

a. the individual Cabilly 1 vectors separately containing a light or heavy chain; or

b. a modified Cabilly 1 vector encoding both an immunoglobulin light and heavy chain for independent expression of these chains.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to modify the Cabilly 1 patented invention so as to cotransform a single host with two vectors each containing DNA encoding a light or heavy chain, or to utilize a single vector containing both light and heavy chain DNA in order to transform a host cell to independently express said DNA sequences as in Cabilly 2 patent claims *1, 15, 18, 21 and 33* (and claims dependent thereon).

The *Moore* patent reference provides *further motivation* to co-express (using one or two vectors) the Cabilly 1 patented light and heavy antibody chains comprising variable regions in a host cell with a reasonable expectation of producing an assembled functional antibody.

Moore et al. disclose and claim a hybrid DNA strategy for the preparation of specific binding polypeptides comprised of two different polypeptide chains, which together assume a conformation having high binding affinity to a predetermined ligand or haptenic site thereof (see e.g. Moore '545, col. 2, lines 39-52). One or both of the different polypeptide chains derived from the variable region of the light and heavy chains of an immunoglobulin may be used to provide specific binding analogous to the binding site of an immunoglobulin, with the composition being referred to as an "rFv" and with the portions corresponding to L-rFv (variable light region of an antibody) and H-rFv (variable heavy region of an antibody), thus forming a functioning single chain antibody (compare to instant patent "Fab proteins" or "univalent antibodies": Cabilly '415 patent col. 5, lines 17-28).

For example the Moore Patent claims:

> 1. A host cell which expresses a recombinant double-chain antibody fragment (rFv) comprising two polypeptide chains having substantially the same amino acid sequence of at least a portion of the variable region, without constant region amino acids, of a mammalian immunoglobulin, the immunoglobulin having binding specificity to a predetermined ligand, wherein the polypeptide chains are prepared by expression of a DNA sequence coding for the variable region, said expression occurring in the absence of expression of a DNA sequence coding for a natively associated constant region, and wherein the two polypeptide chains combine to form the rFv which has a high affinity and specificity for the predetermined ligand.

2. A method of synthesizing an rFv fragment comprising:

(1) cloning first and second DNA molecules respectively encoding heavy and light chains from a hybridoma producing an antibody to a predetermined ligand;

(2) tailoring the cloned DNA molecules to express fragments comprising 95-125 amino acids of the heavy and light chain variable regions, without constant regions, in a host cell;

(3) inserting the tailored DNA molecules into an expression vector in proper relationship with transcriptional and translational regulatory signals in the vector;

(4) transforming the host cell with the expression vector and growing the host cell, whereby the light and heavy variable region polypeptides are expressed and associate to form an rFv having substantially the same binding specificity for the predetermined ligand as the antibody from the hybridoma.

Accordingly, the Moore patent discloses and claims a method of making an "immunologically functional immunoglobulin fragment" (as in instant claims 1, 21 and 33 and dependent claims thereon) comprising independently expressing in a host variable heavy and light chain domains (e.g. rFV including heavy chain gamma and light chain kappa as in instant claims 23-25: see col. 1, lines 33-42; col. 3, lines 59-63; col. 17, lines 4-8) lacking constant regions. Additionally, Moore teaches a "host cell" transformed with a single genetic construct (e.g. pBR322: see e.g. Moore at col. 5, lines 32-35 and col. 7, lines 39-50) or two separate constructs comprising DNA (e.g. ds cDNA derived from a hybridoma as in instant claim 14: see Moore patent claim 2) encoding variable light and heavy chains [E.g. see Moore patent claim 1; col. 10, lines 1-5; col. 23, lines 35-45 (pBR322); and col. 24, lines 50-60 (pGM1L and pGM1H); col. 11, lines 5-12], thus rendering obvious *claims 1-5, 14-18, 21, 23-25, 33.*

One of ordinary skill in the art would be further motivated to utilize the Moore process to make antibodies (e.g. chimeric, humanized as in Cabilly 1) since this represents another solution to the problem faced by Moore of in vivo immunogencity resulting from the use of antibodies comprising constant chains in *in vivo* diagnosis or therapy. Moore's solution was to employ single-chain antibodies lacking constant regions. See Moore at col. 1, lines 64-col. 2, lines 8.

The Moore patent further teaches "appropriate host cells" including non-secreting gram negative bacteria (e.g. *E. Coli*: which form intracellular rFV precipitates requiring lyses, denaturant solubilization and refolding as in instant claims 6-7, 10, 26-28, 30 and 32: see Moore at col. 10; bottom of col. 24-col. 25, line 27) as well as eukaryotic secreting hosts (e.g. *S. cerevisiae* or yeast as in instant claims 6-7, 9, 29: see e.g. Moore col. 5, lines 47-52) from which functioning rFV is recovered (as in instant claim 31). See also Moore patent claims; col. 3; col. 10, lines 8-30 and 39-55; col. 11 and examples). Moore additionally teaches the diagnostic and therapeutic use of their isolate rFV antibodies by labeling the variable light and/or heavy chains with diagnostic labels (e.g. fluorescent "label") or "hazardous labels" (e.g. radioisotopes and toxins as a "drug") for therapeutic use in mammalian subjects (as in instant claims 34-36). See Moore Abstract; col. 3; and columns 25-26. Thus Moore further renders obvious *instant claims 6-7, 9-10, 26-32 and 24-36.*

ii. The prior art provides further motivation to make active antibody with a reasonable expectation of success.

The *Deacon* and *1981 Valle* references introduced and expressed exogenous light and heavy chains into eukaryotic cells achieving assembled functional immunoglobulins.

Additionally, the *Ochi* reference restored specific antibody production by cloning light immunoglobulin chain into a cell line endogenously producing heavy immunoglobulin chain.

More specifically, *Deacon* teaches injecting mRNA encoding heavy and light immunoglobulins (to hemocyanin or ferritin antigen) into *Xenopus* (frog) oocytes (see Abstract; and page 818 for procedure) and concludes (page 829, lines 1-5) that "mRNA from hyperimmunized rats, when injected into oocytes, is translated into heavy and light chains" and that "in oocytes, heavy and light chains can be assembled into immunoglobulin molecules, which can behave as antibodies directed against antigen".

Similarly, *1981 Valle* taught that microinjection of mRNA encoding light (kappa) and heavy (gamma 1) chains from immunoglobulin MOPC21 (produced by mouse plasmacytoma P3/X63 cell line) into Xenopus oocytes resulted in oocyte assembly and secretion of tetrameric mouse immunoglobulin upon addition of horse serum to the oocyte medium to prevent "gratuitous oxidation". See *Valle* Abstract, page 338, col. 2; page 339, col. 2; and Figure 2B, Track 4 showing secreted tetrameric antibody.

Although the above-discussed *Deacon* and *1981 Valle* references utilize m-RNA, as compared to the use of vector DNA in the Cabilly 1 claims for encoding the corresponding light and heavy immunoglobulin chains, once the m-RNA or vector DNA is expressed, the ability of the two chains to assemble into an immunoglobulin does not

depend on the genetic material used for such expression. Accordingly, the difference between using vector DNA vs. mRNA for host transformation is not substantive.

Additionally, *Ochi* discloses that an exogenous light immunoglobulin chain specific for 2,4,6-trinitrophenyl (TNP) cloned into a mammalian cell (mutant igk-14 producing heavy chain specific for TNP but not light chain) results in the cell's assembly and secretion of a functional immunoglobulin (i.e. binds TNP). See Abstract; Figures 1 and 2; last full paragraph on page 340; and Table 1).

Accordingly, the *Deacon, 1981 Valle* and *Ochi* references taken separately or in combination provide further motivation to perform the Cabilly 1 patented steps in a single host cell for producing a chimeric heavy and light chain which is assembled into active antibody thus rendering obvious the production of a functional immunoglobulin with a reasonable expectation of success to one of ordinary skill in the art at the time the instant invention was made.

The *Moore* patent reference teaching of the use of vector(s) comprising variable regions of the heavy and light chain expressed in a host cell to achieve active single chain antibodies provides *further motivation* that additionally including the constant regions would result in the *successful production* of an antibody (e.g. chimeric).

The *Moore* patent teaching in conjunction with the Cabilly 1 patent teaching as applied to the below Cabilly 2 patent claims, as discussed *supra, is* herein incorporated by reference.

***Obviousness of Dependent Claims* 5-10, 12, 14, 19-20, 22, 26-32 and 34-36**

The Cabilly 1 patent claims render obvious dependent claim 5-10, 12, 14, 19-20, 22, 26-32 and 34-36 for the following reasons.

The Cabilly 1 patented invention teaching **differs** from the instant claims by:

a. using vector plasmid pBR322 (claim 5);
b. using bacterial/yeast/mammalian host cells including E Coli strain X1776 (claims 6-8, 19, 20, and 26);
c. secretion from transformed host (e.g. mammalian) of a functional immunoglobulin (claims 9 and 29);
d. insolubilized antibody in the transformed host (e.g. E.Coli) which is solubilized and refolded to form functional immunoglobulin (claims 10 and 27-32)
e. same source for DNA of constant and variable domains (claim 12)
f. mononclonal DNA source of constant and variable domains (claim 14)
g. transforming an anti-CEA antibody (claim 22); and
h. attaching drug or label to the immunoglobulin molecule (claims 34-36).

a Instant claim 5 is obvious

As discussed *supra*, the Cabilly 1 claimed "(replicable) expression vector" is interchangeable with "plasmid" due to the frequent use of these vectors. *Axel* (col. 8, lines 7-35) and *Kaplan* (page 10) teach using plasmids, particularly pBR322, for expressing heterologous proteins thus rendering the use of this particular plasmid species obvious for use in the Cabilly 1 patented recombinant methods.

b. Instant claims 6-8, 19, 20 and 26 are obvious

Claim 6 of the instant patent recites that the host cell is a bacterium or yeast. Claim 7 recites that the host cell is E. coli (a bacterium) or *S. cerevisiae* (a yeast), and claim 8 recites that the bacterial host cell is *E. coli* strain X1776. Claims 19 and 20 recite mammalian host cells. Claim 26 recites that the host cell is E. coli or yeast.

Each of these host cells is a host cell within the scope of claim 1 of the reference Cabilly 1 patent.

Additionally, *Axel* teaches mammalian host cells for expressing proteins, particularly antibodies. *Axel*, col. 5, lines 3-7 and 24-28.

Rice demonstrates expression of a recombinant immunoglobulin light chain in a mammalian host cell. *Rice*, p. 7863. *Kaplan* teaches bacteria and yeast host cells for expressing recombinant immunoglobulin chains (*Kaplan*, p.10, lines 1-33). Thus, the instant Cabilly 2 patent claims 6-8, 19, and 26 are obvious variants of the reference Cabilly 1 patent claims.

c. Instant claims 9 and 29 are obvious

Instant claims 9 and 29 are drawn to expression and secretion of an immunologically functional immunoglobulin.

The reference Cabilly 1 patent claims encompass expressing immunoglobulin proteins in host cells that are capable of secreting immunologically functional immunoglobulins. Cabilly 1 "host cells" include prokaryotic (most preferably the bacteria *E. Coli.*) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See Cabilly 1 patent, col. 8, line 46 to col. 10, lines 13-30, 57. In this regard, the Cabilly 1 patent claims encompass recovery of chimeric light or heavy chains by:

a. cell lysis of insolubilized particles present in the host followed by denaturant solubilization; or

b. host cell secretion of active protein.

See Cabilly 1 patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18.

Axel teaches mammalian host cells for expressing heterologous proteins, including antibodies. See *Axel*: abstract; col. 5, lines 3-7 and 24-28; patent claims 1, 7, 22-24, 28 and 29. *Rice* demonstrates expression of a recombinant immunoglobulin light

chain in a mammalian host cell (*Rice* page 7863). Thus, the selection of host cells capable of secreting proteins for use in the Cabilly 1 patented invention would have represented an obvious design choice in view of the *Axel* and/or *Rice* references.

d. Instant claims 10 and 27-32 are obvious

Instant claims 10 & 27-32 are drawn to expressing insolubilized antibody in the transformed host (e.g. *E.Coli*) that is solubilized and refolded to form immunoglobulin.

The Cabilly 1 patent claims encompass expressing immunoglobulin proteins in host cells (e.g. E. Coli) in insoluble form which is then solubilized and refolded to form functional immunoglobulin. Cabilly 1 "Host cells" include prokaryotic (most preferably the bacteria E. Coli.) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See '567 patent, col. 8, 1ine 46 to col. 10, lines 13-30, 57. In this regard, the Cabilly patent claims encompass recovery of chimeric light or heavy chains by:

a. cell lysis of insolubilized particles present in the host followed by denaturant solubilization; or

b. host cell secretion of active protein.

See Cabilly 1 patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18.

Kaplan teaches bacteria and yeast cells for expressing recombinant immunoglobulin chains (p. 10, lines 1-27) and *Kaplan* also describes rupturing the host cells, isolating the heavy and light chains and combining them under mildly oxidative conditions to promote refolding and disulfide bond formation. See *Kaplan* at page 10, lines 1-33.

Similarly, *Builder et al.* teach expression of exogenous or foreign proteins in host cells (e.g. bacteria) in insoluble form that is recovered, solubilized and refolded. See *Kaplan* columns 2-6 and Schemes 1 and 2.

Thus, the instant patent claims *10 and 27-32* are obvious variants of the reference Cabilly 1 patent claims in view of *Kaplan* and/or *Builder*.

e. Instant claim 12 is obvious

Claim 12 of the instant patent requires that the constant and variable domains be derived from the same source of DNA.

Although the reference Cabilly 1 patent is directed to utilizing DNA encoding heavy or light chains from different sources (e.g. chimeric), it would have been obvious to utilize heavy or light chain DNA from the same source in light of the use of same source DNA as taught by both the *Kaplan* (e.g. from human hybridomas) and/or the *Rice* reference (e.g. from mice), especially since non-chimeric expression was conventional in the art.

f. Instant claim 14 is obvious

Claim 14 of the instant patent requires that the constant and variable domains be derived from one or more monoclonal antibody producing hybridomas.

Kaplan teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains (including variable and constant domains) to specific antigens. By using known biology techniques, the mRNAs can be used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins (see *Kaplan* page 3, lines 4-9). In addition, *Kaplan* teaches that a variety of host cells (e.g. bacteria and yeast), may be

used to express such recombinant immunoglobulin heavy and light chains (see page 10, lines 1-33). Accordingly, employing monoclonal antibodies as a source of DNA encoding heavy and light chains (variable and constant domains) would have been obvious in light of the *Kaplan* teaching.

g. *Instant claim 22 is obvious*

Claim 22 of the instant patent limits the method of claim 21 to making an anti-CEA (i.e. an antibody to carcinoembryonic antigen).

CEA is an antigen within the general scope of a "particular known antigen" of the reference Cabilly patent claim 1. Additionally, the instant Cabilly 2 patentee admits that anti-CEA antibodies are useful for tumor detection and perhaps use in treating tumors that have CEA at their surface. See Cabilly 2 patent, col. 16, lines 31-38 and references cited therein.

Additionally, *Accola* et al. describes making anti-CEA monoclonal antibodies.

Accordingly, instant claim 22 represents an obvious variant of the reference Cabilly 1 patented invention in light of the reference Cabilly 1 patented claimed teaching and the art-recognized motivation to make claim 22 CEA antibodies for diagnostic or therapeutic purposes.

h. Instant claims 34-36 are obvious

Claims 34-36 (dependent on 9, 10 and 33) further include attaching a label or drug to the immunoglobulin.

Kaplan (page 8, lines 7-21) teaches the use of antibodies for site directed therapy (i.e. via drug attachment) or diagnostic use (i.e. via label attachment for localization).

Accordingly, it would have been obvious to modify the reference Cabilly 1 claimed antibodies to attach a drug and/or label for use in therapy and/or diagnostics, respectively.

Examiner Rebuttal of Arguments Presented in Patentee's Responses (1/25/05 and October 30, 2006)

1. Patentee argues that the findings of the PTO during prosecution of the '415, '567 and Boss Patents establish that the instant Cabilly 2 ('415) patent claims are patentably distinct from the claims of the reference Cabilly 1 ('567) patent. The Patentee particularly cites the Board's failure to introduce the Cabilly 1 patent claims into the interference between the Cabilly 2 (copied) claims and the Boss patent claims; and additionally an interview conducted on October 4, 2001 during the Cabilly 2 patent prosecution indicating the failure of the Examiner to raise double patenting between the Cabilly 1 and 2 patent claims.

These arguments were considered but not deemed persuasive.

Initially, it is noted that *35 U.S.C. 121* does not preclude obviousness double patenting. See 90/007,542 August 16, 2006 office action at pages 5-6 herein incorporated by reference.

The above argument is not persuasive since substantial new questions of patentability regarding anticipation, obviousness and double patenting are now based on references (or combination of references) which were not considered and/or appreciated by the Examiner in the earlier concluded examination(s) nor by the Board judges in the interference proceeding. MPEP 2258.01.

2. The Patentee (e.g. see Oct. 30, '06 response at pages 32-35) submits the 2nd Dr. Harris (especially items 8-28 general state of the prior art) and the 2nd Dr. Rice (especially items 8-16 directed to lymphocytes) in order to demonstrate the state of the prior art as of early April 1983. In this respect the following difficulties were noted:

a. the lymphocyte antibody producing mechanism was unclear and the ability to control expression of light chain in B lymphocyte cell lines (as in the Dr. Rice PNAS article) was uncertain; and

b. the genetic engineering of relatively small number of recombinantly produced proteins would engender a low expectation of recombinantly producing a multimeric protein such as an immunoglobulin tetramer.

The submitted Declarations and patentee arguments were considered but deemed nonpersuasive for the following reasons:

Initially, it is noted that knowing the mechanism regarding lymphocyte antibody production is helpful but in and of itself does not preclude obviousness and particularly a reasonable expectation of success, since absolute certainty is not required; and knowledge of mechanism is not always complete nor even known prior to practicing a claimed invention.

Additionally, Patentee's analysis of the state of the prior art as of April 1983 regarding genetic engineering in the context of expressing proteins, include complete immunoglobulins (light and heavy chains) or immunoglobulin fragments (variable light and variable heavy chains) is misguided.

An analysis of the claims at issue is the first step in determining if a second invention is merely an obvious variation of the first. See *Georgia-Pacific Corp. v. United States Gypsum Co.*, No. 97-1238, 1999 WL 988547 (Fed. Cir. Nov.1,1999).

As discussed above, the Cabilly 1 patent claims teach a method of preparing a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen. The Cabilly 1 patent claims further teach replicable expression vectors useful for transforming a host cell and the recovery of chimeric heavy or light chains from the host cell culture.

Additionally, the specification can be used in the context of a double patenting rejection as a *dictionary* to learn the meaning of a term in the patent claim. *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999). Further, those portions of the specification which *provide support* for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970).

Accordingly, the Cabilly 1 claimed "(replicable) expression vector" is defined as vectors capable of expressing DNA sequences contained therein which are frequently in the form of plasmids, thus 'plasmid' and 'expression vector' are often used interchangeably. See Cabilly 1 patent col. 8, lines 21-45.

The Cabilly 1 claimed "host cells" include prokaryotic (most preferably the gram (-) bacteria E. Coli. Strains ATCC: 31446 and 31537) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See Cabilly 1 patent , col. 8, 1ine 46 to col. 10, lines 13-30, 57.

The Cabilly 1 claimed means of successfully "recovering the chimeric heavy or light chain from the host cell culture" is determined by the type of protein and host

organism but utilizes art known techniques including cell lysis of insolubilized particles present in the host (e.g. gram-negative E. Coli) followed by denaturant solubilization unless the host organism normally secretes the protein out of the cell (e.g. some yeast and gram positive bacteria). See Cabilly 1 patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18.

Additionally, both the Cabilly 1 and the instant Cabilly 2 patented inventions include claims directed to the same statutory subject matter: recombinant processes, vectors and host cells for making immunoglobulins (particularly chimeric immunoglobulins), and immunoglobulin products. The recombinant procedures used to obtain the DNA sequences, prepare vectors, transform cells, culture cells, and recover the immunoglobulins are the same, whether for recombinant immunoglobulins that mimic naturally occurring ones or for altered recombinant immunoglobulins, such as chimeric antibodies. See e.g., '567 patent, col. 15, lines 59 to col. 16, line 15; and col. 28, lines 44-47. Thus, the scope of vector and host cells applicable to the Cabilly 1 patented method are equally applicable to the instant Cabilly 2 method as well as the means of obtaining the expression vectors for expressing a light or heavy (chimeric) antibody chain in these host cells.

Accordingly, the Cabilly 1 patented method as directed to the making of vectors (e.g. cDNA) encoding mammalian light and heavy chains and their expression separately in host cells, including prokaryotic and eukaryotic host cells, is part of the state of the prior art as of 1983.

In this regard, it is noted that patent owner admissions in the record as to matters affecting patentability may be utilized in a reexamination proceeding (see 37 CFR 1.104(c)(3).), including the use of declarations which address any of the obviousness criteria under *Graham v. Deere* including reference interpretation and the state of the prior art. See MPEP 2258 (case law cited therein). Additionally, admissions (e.g. background references) or references provided in the Cabilly 1 patent disclosure are evidence as to the state of the prior art as of 1983.

The Cabilly 1 patent disclosure describes the "state of the prior art"" as follows:

> Recombinant DNA technology has reach sufficient sophistication that it includes a repertoire of techniques for cloning and expression of gene sequences. Various DNA sequences can be recombined with some facility, creating new DNA entities capable of producing heterologous protein product in transformed microbes and cell cultures. The general means and methods for the in vitro ligation of various blunt ended or "sticky" ended fragments of DNA, for producing expression vectors, and for transforming organisms are now in hand. ... In practice the use of recombinant DNA technology can express entirely heterologous polypeptides- so called direct expression-or alternatively may express a heterologous polypeptide fused to a portion of the amino acid sequence of a homologous polypeptide. .... The art of maintaining cell or tissue cultures as well as microbial systems for studying genetics and cell physiology is well established. Means and methods are available for maintaining permanent cell lines, prepared by successive serial transfers from isolated cells. For use in research, such cell lines are maintained on a solid support in liquid medium, or by growth in suspension containing support nutriments. Scale-up for large preparations seems to pose only mechanical problems. See Cabilly 1 patent '567, col. 4, lines 8-54.

As admitted in the patentee submitted "Declaration of Dr. Richard Axel" (attached) provided in the related 08/422,187 [1] patent application in response to an enablement rejection, the Cabilly 1 patent specification examples drawn to a procaryotic

[1] The 08/422,187 application is a continuation of 07/205,419 application which is the instant patent undergoing reexamination.

E. coli host cell expression of individual immunoglobulin chains (i.e. Cabilly 1 patented expression) is applicable to a variety of other host cells (e.g. yeast, VERO, HeLa, Chinese Hamster Ovary or CHO, W138, BHK, COS-7 and MDCK) and recombinant vectors available to the skilled artisan as of April 1983 (see also 1983 or earlier reference cited therein).

Thus, the state of the art as of April 1983 available to the skilled artisan includes the above background teaching as well as the additional prior art teachings provided in the prior art rejection references discussed above (including Axel, Rice, Kaplan, Dallas, Moore, Deacon, Valle 81/82, Oi, Ochi, Builder and Accolla) which are directed to the recombinant expression and/or recovery of one or more heterologous proteins (including immunoglobulins and their Fv or Fab fragments) in prokaryotic and eukaryotic hosts.

3. Patentee presents a 132 Declaration by Dr. Riggs in order to establish that the separate recombinant production of immunoglobulin light or heavy chains was useful to raise monospecific antisera for diagnostic use, such as to clinically diagnose and monitor multiple myeloma. Additionally, in the 132 Declaration Dr. Timothy John Roy Harris provides his opinion that the phrase "having specificity for a particular known antigen" in the reference Cabilly 1 patent "does not mean that the individual chimeric immunoglobulin chain must exhibit-by itself-antigen binding functionality, or that the chimeric chain must be incorporated into an immunoglobulin molecule or immunologically functional fragment. Patentee also states that the disclosure of the Cabilly 1 patent claims can only be used for definitional purposes in order to interpret the meaning of an unclear claim term or element. Accordingly, it is argued that the Cabilly 1 disclosure regarding utility is not prior art knowledge available for purposes of motivation.

These arguments were considered but not deemed persuasive.

The specification can be used in the context of a double patenting rejection as a dictionary to learn the meaning of a term in the patent claim. *Toro Co. v. White Consol.*

Indus., Inc., 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999) "[W]ords in patent claims are given their ordinary meaning in the usage of the field of the invention, unless the text of the patent makes clear that a word was used with a special meaning."). The ordinary and customary meaning of a term may be evidenced by a variety of sources, including "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Phillips v. AWH Corp.*, 415 F.3d at 1314, 75 USPQ2d at 1327. Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970).

In attempting to clarify the meaning of the phrase "having specificity for a particular known antigen", the patentee (page 22 of Oct. 30 2006 amendment in 90/007,542 proceeding) refers to the definition of the term "chimeric" as it refers to "chimeric antibodies" (i.e. light or heavy antibody chains in which the variable and heavy chains are derived from different species). Further, as argued by patentee (page 23 of Oct. 30 2006 amendment), the 1st Dr. Harris Declaration defines the same phrase as referring to deriving "from the variable domains of an antibody or an antibody fragment exhibiting an antigen binding function".

In helping to define the phrase "having specificity for a particular known antigen", the Examiner pointed to the reference Cabilly 1 patent (col. 1, lines 30-35; and col. 1, lines 14-23) that describes two types of immunoglobulins:

a. non-specific immunoglobulins which lack antigen specificity and are "produced at low levels by the lymph system and in **increased levels by myelomas"** (emphasis); and

b. immunoglobulins containing assemblies of light and heavy chains which have specific immunoreactive activity.

In light of the Cabilly 1 patent's claimed teaching of the ability to separately make light and heavy chains which each possess variable regions "having specificity for a particular known antigens" it is reasonable to one of ordinary skill in the art to interpret this phrase as *suggesting* the use of the Cabilly 1 claimed immunoglobulins for assembly into antibodies, in contradistinction to the alternate use of immunoglobulins for the diagnosis of myeloima.

This interpretation is supported by the fact that both the reference Cabilly 1 and instant patent claims encompass both utilities unless the claims specifically recite otherwise. It is also supported by patentee's own argument which defines the term "chimeric heavy or light chain" by reference to the definition of a "chimeric antibody". Accordingly, the Examiner is not improperly importing specification utilities into the claims or relying on the specification for motivation as asserted by the patentee.

4. The 1st and 2nd Harris 132 Declarations argue that the Axel reference does not suggest processes for producing and isolating multiple different polypeptides from a transformed host cell but only a single protein (encoded by DNA I) and a selectable marker (encoded by DNA II). Thus it is argued that Axel does not teach (nor can it be modified to teach) encoding both a light and heavy chain protein in a transformed host cell. It is further argued that the Axel reference although mentioning "antibodies" as exemplified polypeptide, fails to disclose procedures for producing immunoglobulin molecules or immunologically functional fragments having both heavy and light chains. Accordingly, where DNA I is drawn to an antibody, this should be interpreted to be a light or heavy chain but not both. The Axel embodiment drawn to "a multiplicity of foreign DNAI molecules" is argued to be limited to producing multiple copies of the same (and not different proteins).

These arguments were considered but not deemed persuasive.

Initially it is noted that in response to patentee's arguments against the reference(s) individually, one cannot show nonobviousness by attacking reference(s) individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The patentee's arguments fail to address the *combined* reference teaching by Axel of co-expressing two separate proteins (an exogenous gene of interest and an exogenous reporter gene) in a single eukaryotic (mammalian cell) in the context of producing an antibody with the Cabilly I patent teaching of the separate expression of heavy and light chains.

It is also noted that the selection of an antibody as one or more (multiplicity) of the foreign protein(s) encoded by DNA I is a *patented* embodiment (see Axel patent claims 7, 23, 29, 37, 60 etc.).

As such, the Axel patent claims enjoy a presumption of validity once issued (see 35 U.S.C. § 282) and a party seeking to invalidate a patent claim must provide "clear and convincing" evidence of invalidity to overcome this presumption. Additionally, cited

references are presumed to be operable and enabled, and the patentee must provide evidence (not argument) to rebut this presumption. See MPEP § 2121 at 2100-64 to 2100-67.

Further, the threshold for enabling a reference for purposes of prior art is much lower than the threshold for enablement under 35 USC 112, first paragraph required for a patented invention insofar that the prior art reference need not demonstrate efficacy or utility. See e.g. in *Rasmusson v. Smithkline Beecham Corp.* 75 USPQ2d 1297 (Fed. Cir. 2005); and *Impax Labs., Inc. v. Aventis Pharmaceuticals, Inc.*, No. 05-1313 (Fed. Cir. Nov. 20, 2006) concurring with the *Rasmusson* holding.

In this regard, the Axel reference suggests expressing two immunoglobulin chains in a single eukaryotic host cell, since Axel discloses and claims encoding an antibody that necessarily possesses both light and heavy immunoglobulin chains. The Axel reference clearly encompasses one *or more* genes which encode one or more proteins: e.g. "... DNA which includes a gene **or genes** coding for desired proteinaceous materials ..." (Abstract lines 1-4, with emphasis). Accordingly, Axel's patented multiplicity of foreign proteins could be interpreted to encompass the expression of the same or different (e.g. a light and/or heavy antibody chain) proteins.

5. The patentee presents the 132 Declaration of Dr. Douglas A. Rice to explain the relevance of the Rice and Baltimore, PNAS USA 79:7862 (1982) reference applied by the Examiner in the prior obviousness double patenting rejection. In this regard Dr. Rice explains that the reference's purpose was to gain a better understanding of mechanisms by which differentiated B cells regulate immunoglobulin expression; and that the reference does not explain how one might produce exogenous heavy and light chain in the 81A-2 strain which already endogenously produced heavy chain. Further, the Declarant argues that the reference's Ig tetramer was not properly assembled to produce a functional antibody.

These arguments were considered but not deemed persuasive for the following reasons.

Initially it is again noted that in response to patentee's arguments against the reference(s) individually, one cannot show nonobviousness by attacking reference(s) individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Additionally, patentee's arguments are not commensurate to those instant Cabilly patent claims that are not specifically limited to the feature upon which patentee relies (properly assembled "functional" antibody). The term "immunoglobulin" in the instant methods, as discussed in the above claim interpretation section, represents a generic term that encompasses both specific (i.e. antibodies) and non-specific immunoglobulin proteins e.g. produced at low levels by lymph or myelomas. See Cabilly 2 '415 patent col. 1, lines 23-43. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further, the Rice reference clearly teaches to one of ordinary skill in the art that an exogenous immunoglobulin light chain assembles with a heavy chain endogenously produced by the cell even though both chains possess *different* antigen specificity. Thus, in light of this teaching it would be reasonable for one of ordinary skill in the art to expect that expressing a light and heavy chain of the *same* antigen specificity (e.g. derived from a known antibody) in a competent host would result in the assembly of a functional antibody. See Declaration of David Baltimore submitted by the 3rd party with the 2nd Request for Reexamination.

6. Patentee argues that the '415 Cabilly 2 patent claims require that the encoded heavy and light chain polypeptides be expressed as "separate molecules" which stems from the requirement for independent expression of the introduced DNA sequences . See Oct. 30, 2006 page 30 Amendment.

This argument is not persuasive for the following reasons.

None of the references of record teach or suggest expressing the light and heavy chains as a fusion protein as implied by the patentee since utilizing this construct would make assembly of the light and heavy chains prohibitive. In fact, the prior art references of record clearly teach the independent expression of the light and heavy chains in all host systems. See e.g. Axel for separate expression of heterologous proteins in a single eukaryotic host; Moore and Kaplan teaching of the making of single chain antibodies in bacteria (e.g. *E.Coli.*) with equal applicability to eukaryotes (yeast) and mammals that secrete the antibody; and Rice, Deacon, Valle, Oi and Ochi for independent expression in secreting mammalian hosts.

7. Referring to the Axel, Rice, Kaplan or Dallas references, the Patentee (along with the 2nd Dr. Harris and 2nd Dr. Rice Declarations) argue that it is "striking" that none of these references expressly teach producing immunoglobulin molecules or functional fragment by independently expressing, in a single host cell, DNA sequences encoding both light and heavy immunoglobulin chains". See Oct. 30, 2006 amendment page 39.

These arguments were considered but not deemed persuasive.

Patentee's argument that the Axel, Rice, Kaplan or Dallas references fail to expressly teach (i.e. anticipate) the instant invention is not at issue. In the above double patenting obviousness rejection the combination of these cited reference are relevant with respect to obviousness and not anticipation.

In this regard, it is noted that the newly submitted Moore patent reference does expressly teach the independent expression of variable light and variable heavy chains in a single host to produce a functional single chain immunoglobulin fragment within the scope of the instant claims.

8. Regarding the Kaplan reference, patentee argues (See Oct. 30, 2006 amendment pages 53-54) that Kaplan fails to suggest production of multiple immunoglobulin chains in one transformed host cell. The suggestion regarding construction of recombinant DNA molecules containing either an antibody heavy chain or an antibody light chain gene, expressing these genes in separate cells, and assembling the light and heavy chain proteins is not supported by experimental results, examples or specific guidance regarding these methods of producing a heavy or light immunoglobulin chain polypeptide. See Harris Second Declaration, ¶ 69.

This argument is not persuasive for the following reasons:

Attacking an obviousness rejection relying on the combined teaching of multiple references by piecemeal analysis of the Kaplan reference is not persuasive.

Accordingly, the failure of the Kaplan reference to teach single host cell antibody expression using its recombinantly produced heavy and light chains is not persuasive.

Additionally, as discussed in the above obviousness rejection, Kaplan teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains to specific antigens. By using known molecular biology techniques, the mRNA's can be used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins (see page 3, lines 4-9). In addition, *Kaplan* teaches that a variety of host cells (e.g. bacteria and yeast) and plasmids (particularly pBR322) may be used to express recombinant heavy and light chains (see page 10, lines 1-33).

Accordingly, although Kaplan fails to specifically exemplify the recombinant making of antibodies, Kaplan nevertheless provides a road map to one of ordinary skill in the art as to how to do so. Thus, the teaching of Kaplan is not limited to dependent claims drawn to the use of hybridomas, plasmids or host cells (as implied by the patentee), but is additionally relevant regarding enabling the suggestive teaching of the other references regarding co-expressing light and heavy chains in a host cell (prokaryotic, eukaryotic or otherwise) to obtain an assembled antibody capable of binding its corresponding antigen.

9. Regarding the Dallas reference, patentee (See Oct. 30, 2006 amendment pages 54-56) and the Dr. Rice declaration (item 42) argue that Dallas is limited to teaching the expression of bacterial genes in bacterial host cells (E.Coli) which differs from the expression of eukaryotic genes in bacterial cells. Eukaryotic immunoglobulin genes are more complex than bacterial genes which lack introns and bacterial gene control elements and translational control elements were far better characterized and understood in early 1983 relative to eukaryotic systems. Additionally, the proteins produced by Dallas are apparently not secreted by or recovered from the host cells.

In response to patentee's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As pointed out in the above rejections *Dallas* teaches that two different proteins (in addition to a selectable marker) can be expressed in a single host cell and such expression may be accomplished by the use of two vectors, each containing DNA encoding one of the proteins, or by use of a single vector that contains DNA encoding each of the proteins.

Accordingly, the Dallas reference is relevant toward modifying the Cabilly 1 method to co-express (using one or two vectors) a light and heavy antibody chain.

Additionally, the Dallas reference provides support for the Axel reference teaching of eucaryotic expression of both a light and heavy antibody chains along with the reporter gene for producing an antibody. In this regard Axle specifically provides motivation to utilize eukaryotic hosts, in preference to prokaryotic hosts (as in Dallas), for expressing two or more exogenous proteins.

10. Patentee states that the Examiner improperly relies upon a 3rd Party Opinion Declaration of Dr. David Baltimore (that "he and others working in the field would have expected that if two chains were expressed they would form a functional antibody ...") in an Ex Parte Reexamination since the Reexamination statute limits the determination of a Substantial New Question of Patentability (SNQ) to "patents and printed publications" (citing In re Lonardo). Additionally, the Patentee, along with the 2nd Harris and 2nd Rice Declarations, argue that Dr. Baltimore's conclusory and unsupported opinions are not representative of one of ordinary skill in the art, since he is deemed "extraordinary" (Nobel Laureate) and in view of his "unique perspective". See Oct. 30, 2006 Amendment at pages 51-53; 2nd Declaration of Dr. Rice items 46-58.

These arguments were considered but deemed nonpersuasive.

Initially, it is noted that:

> "[A]ffidavits or declarations (or other written evidence) which explain the contents or pertinent dates of prior art patents or printed publications in more detail may be considered in reexamination, but any rejection must be based upon the prior art patents or printed publications as explained by the affidavits or declarations >or other written evidence. The rejection in such circumstances cannot be based on the affidavits or declarations (or other written evidence) as such, but must be based on the prior art patents or printed publications. See MPEP 2258 E: "Affidavits or Declarations or Other Written Evidence"

Additionally, it is proper to submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991);MPEP 2164.05.

The above-recited rejections are proper as they rely solely on patents and printed publications and not Dr. Baltimore's Declaration. The use of Dr. Baltimore's declaration is proper since it is being offered only to explain the interpretation of the contents of a

prior art printed publication (i.e. the Dr. Rice 1982 PNAS article) to one of ordinary skill in the art.

Regarding, the weight to be afforded Dr. Baltimore's 132 Declaration the following is noted:

It is admitted that "one of ordinary skill in the art" as of early April 1983 is "a Ph.D. in molecular biology or a related field, and about two years of post-doctoral experience in a lab working with recombinant DNA." See 2nd Dr. Rice Declaration item 8.

Both Dr. Rice and Dr. Baltimore clearly qualify as "one of ordinary skill in the art" and both are authors of the 1982 PNAS article and thus share the same "unique perspective" regarding the subject matter presented thereto. Accordingly, comparable weight is being afforded their respective opinions in light of evidentiary evidence provided by them and in light of the teaching of the 1982 PNAS article.

Dr. Rice and Dr. Baltimore appear to be in agreement that the studies in the PNAS article provide a demonstration that a functional kappa (light chain) gene can be introduced into a lymphoid cell line in which it is continuously expressed (Dr. Rice Declaration item 55; and Abstract of article).

However Dr. Rice disagrees with the following Dr. Baltimore statement:

> ... in light of our demonstration that an introduced light chain gene encoded a protein that would combine with an endogenous heavy chain, without further testing of the idea I and others working in the field would have expected that if two chains were expressed, they would form a functional antibody". See Dr. Baltimore declaration at item 5.

Dr. Rice argues that the PNAS article fails to "clearly demonstrate" that the endogenous heavy chain and the recombinant light chain assembled into a proper tetramer made up of two heavy chains and two light chains. 2nd Dr. Rice Declaration item 64.

Although Patentee' Response and accompanying Declarations point out that the immunoglobulin produced in Rice was not demonstrated to be functional it is noted that the independent claims of Cabilly 2 do not recite that the immunoglobulin is necessarily "functional" (in contradistinction to the fragment).

Additionally, in accordance with recent CAFC caselaw a prior art reference for purposes of rejection under 35 USC 102/103 (in contradistinction to an enablement rejection under 35 USC 112) need not demonstrate efficacy or utility. See e.g. in *Rasmusson v. Smithkline Beecham Corp.* 75 USPQ2d 1297 (Fed. Cir. 2005) ; *Impax Labs., Inc. v. Aventis Pharmaceuticals, Inc.*, No. 05-1313 (Fed. Cir. Nov. 20, 2006) concurring with the *Rasmusson* holding.

Accordingly, the prior art of record for purposes of anticipation or obviousness need only suggest the instant method of making an antibody in a single host, with at most, a reasonable expectation regarding its ability to bind antigen.

The Rice reference clearly teaches that an exogenous immunoglobulin light chain produced in a cell (mammalian) *assembles* with an endogenous heavy chain produced *in the cell* producing an immunoglobulin.

Accordingly, such a teaching by the Rice reference would reasonably suggest to one skilled in the art that expressing a Cabilly 1 exogenous heavy chain and light chains

in a single cell, would resulting in an *assembled immunoglobulin*, even if the chains are *from different immunoglobulins* with *different specificities*.

Further, in light of the Rice article teaching, the use of light and heavy chains from similar sources and particularly the use of chains with the same (or similar) antigen specificities would not only assemble, but also would reasonably be expected to achieve a functional assembled immunoglobulin (e.g. possess some degree of antigen binding function).

Thus, in view of the evidence, Dr. Baltimore' opinion regarding the reasonable expectation of those skilled in the art regarding the expression of light and heavy chains in a single host cell (mammalian) is credible.

11. Regarding the Ochi and Oi articles Patentee (e.g. see Oct. 30, '06 response especially pages 38-41), the submitted 2nd Harris Declaration (items 79-86 addressing Ochi/Oi) and the submitted 2nd Rice Declaration (items 21-26) argue that Ochi is at best cumulative to the Rice 1982 PNAS paper since it uses a cell line that was already producing an endogenous light chain protein. Even though the Ochi experimental protocol was more certain (than the PNAS lymphocyte line) since their host cell retained the ability to endogenously produce heavy and light chain (2nd Rice Declaration: item 21), Ochi nevertheless achieved "abnormal levels of expression". The Oi report of "varying levels of expression" in their hybridoma cell lines is argued to cast doubt on the ability to successful express antibody heavy and light chains. Additionally, the functional assembly of an immunoglobulin tetramer in lymphocytes is questioned especially in view of the lack of information regarding the control of light chain expression levels in lymphocytes.

The above arguments were considered but deemed nonpersuasive.

Initially, it is noted that piecemeal analysis of reference(s), which are not solely relied upon for obviousness, is not persuasive. Additionally, patentees arguments, along with the submitted declarations addressing lymphocyte or hybridoma expression is not

commensurate to the instantly claimed invention drawn to a generic of host cells including prokaryotes (e.g. *E. Coli.*), eukaryotes (e.g. yeast) including mammals.

In any event, patentee's arguments fail to refute the Ochi teaching of achieving expression of an assembled functional (specific for TNP) secreted immunoglobulin from a transformed mammalian cell incorporating an exogenous light chain (specific for TNP). Thus, Ochi teaches that an exogenous immunoglobulin chain that is produced in a mammalian cell is capable of combining in a cell with its corresponding endogenously produced immunoglobulin chain resulting in an assembled immunoglobulin that is secreted from the cell which is specific for its corresponding antigen.

Further, patentees arguments fail to refute the Oi teaching of producing an assembled immunoglobulin by transforming a mammalian cell (a hybridoma) with a vector encoding an immunoglobulin light chain resulting in the expression of a light chain which assembles with an endogenous immunoglobulin heavy chain to produce an assembled immunoglobulin that is secreted from the cell.

Accordingly, the Ochi and/or Oi references, taken separately or in combination with the other cited prior art provide motivation for and engender a *reasonable expectation* to co-transform a single mammalian cell with appropriate light and heavy antibody chains to achieve a secreted, assembled, and functional immunoglobulin. The instant patent claims do not require ideal transformation; nor is *absolute success* the criteria for obviousness.

12. Regarding the Deacon ('82 Valle cumulative) and '81 Valle references, patentee (e.g. see Oct. 30 '06 response at page 38-62), the submitted Dr. Colman Declaration (coauthor of the Valle 1981 and 1982 articles) and 2nd Dr. Harris Declaration (items 87-97) argue that these references employ an "experimental model system" (the *Xenopus* oocyte cell) which is an undifferentiated frog egg cell which upon fertilization differentiates into all the different types of cells. As such it is argued that Xenopus oocytes which employ messenger RNA (mRNA) are not representative of the instantly claimed "host cells" in light of their special capacity to translate mRNA relative to differentiated cells utilizing a vector. Thus, one skilled in the art would not consider frog cells, "host cells" within the meaning of the instant claims.

These arguments are not persuasive for the following reasons:

As defined in the Cabilly 2 patent (col. 8, lines 26-28), "Host cells," include prokaryotic or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See '567 patent, col. 8, line 46 to col. 10, 1ines 13-30, 57. Accordingly, frog (as amphibians, vertebrates) eggs are within the scope of the instantly claimed "host cells".

Turning to the references, the 1982 Valle and Deacon references are cumulative in their teaching of microinjection of mRNA encoding light and heavy immunoglobulin chains into Xenopus oocyte cells (i.e. a single cell) to produce secreted active antibody.

Deacon and 1982 Valle, therefore, teach that a single cell can be modified to include genetic material encoding an immunoglobulin heavy chain and an immunoglobulin light chain and that once expressed assemble into a functional immunoglobulin.

Similarly, the 1981 Valle reference teaches the production and secretion of tetrameric immunoglobulin molecules from *Xenopus* oocytes introducing (i.e. a single cell).

Based on such teachings, it would have been obvious to one skilled in the art to perform the Cabilly 1 patented method in a single host cell to produce an immunoglobulin.

Additionally, the teaching of each of Deacon, 1981 Valle and 1982 Valle does not depend upon the genetic material used for such production, since once expressed, the ability of the two chains to assemble into an immunoglobulin does not depend on the genetic material used for such expression. Recombinant production of an exogenous protein necessarily involves transcription of the exogenous DNA to produce exogenous mRNA. The exogenous mRNA is then translated into exogenous protein. See also 1982 Valle 2 Abstract.

In this regard, patentee has failed to prove that successful transformation using an undifferentiated eucaryotic host cell (i.e. *xenopus* oocyte) would not be *reasonably expected* to work in a differentiated eukaryotic cell in an analogous manner.

Moreover, it is noted that patentee's past action during an opposition proceeding in Europe undermines patentee's present argument. In Europe, one of the owners of Cabilly 2 (Genentech, Inc.) opposed a European patent granted to Celltech Limited (the "Boss Patent") that contained the following claim:

> A process for producing a heterologous Ig molecule or an immunologically functional Ig fragment in a single host cell, which comprises transforming the host cell with separate DNA sequences respectively encoding polypeptide chains comprising at least the variable domains of the Ig heavy and light chains and expressing each of said polypeptide chains separately in said transformed single host cell. [See Appendix C, p. 1, A.1.1 provided by the 3rd party requester in the 90/007,859 proceeding]

The challenged Boss patent claim is essentially identical to claim 1 of the instant invention and in the opposition, Genentech asserted that the Boss claims were not patentable (lacked novelty or inventive step) over the 1982 Valle reference teaching. In particular, Genentech stated:

> 2.3 Accordingly, Document 2 (Valle) clearly teaches the production of an immunologically functional heterologous immunoglobulin molecule in eukaryotic cell transfected by separate DNA molecules encoding its heavy and light chains, respectively. In view of the broad implications evidenced by the Abstract, the fact that the actual experiment was performed with microinjected mRNAs is not relevant. In any event, because the messenger RNA carries the information from DNA to the ribosomal sites of protein synthesis, it is functionally equivalent to DNA.

Accordingly, the patent owner's use in the opposition of the Valle reference teaching against claim(s) analogous to those of the instant patent would constitute an admission that the expression of an immunoglobulin in an undifferentiated eucaryotic host cell (i.e. xenopus oocyte) would be correlative to a host cell within the scope of the instantly claimed invention.

13. Regarding, the Kaplan,Builder and Accola references and the dependent claim limitations (e.g. claims 10, 14, 22 and 27-32) Patentee argues that these (e.g. see Oct. 30 '06 response at pages 67-69) references are not directed to transforming or refolding of immunoglobulin heavy and light chains.

In response to patentee's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.

1986). The above-discussed obviousness double patenting rejection(s) address the application of these references to the instant claim limitations.

14. Regarding dependent claim 12, patentee argues that the Cabilly 1 patent teaches chimeric (different source light and variable chains) antibodies and no prior art evidence renders obvious the use of same source constant and variable chains (e.g. see Oct. 30 '06 response at pages 68-69).

This argument is not persuasive because the obviousness double patenting rejection(s) discussed above provide a rationale for the obviousness of claim 12 combining the Cabilly 1 patent claims with the secondary prior art references (e.g. Kaplan, Rice and Moore).

Conclusion

Claims 1-36 of U.S. Pat. No. 6,331,415 are rejected.

1. **THIS ACTION IS MADE FINAL.** Patent Owner's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on December 14, 2006 (Moore 5,840,545 patent reference) prompted the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 609.04(b); 706.07(a).

A shortened statutory period for response to this action is set to expire two months from the mailing date of this action. **Extensions of time under 37 CFR 1.136(a) do not apply in reexamination proceedings. Extensions of time in reexamination proceedings are provided for in 37 CFR 1.550(c).** A request for extension of time must be filed on or before the day on which a response to this action is due, and it must be accompanied by the petition fee set forth in 37 CFR 1.17(g). The mere filing of a request will not effect any extension of time. An extension of time will be granted only for sufficient cause, and for a reasonable time specified.

The filing of a timely first response to this final rejection will be construed as including a request to extend the shortened statutory period for an additional month, which will be granted even if previous extensions have been granted. In no event, however, will the statutory period for response expire later than SIX MONTHS from the mailing date of the final action. See MPEP § 2265.

Patent Owner Amendment

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

Ongoing Duty To Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,331,415 throughout the course of this reexamination proceeding. The third party requester(s) is (are) also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah D. Jones can be reached on 571-272-1535.

All correspondences relating to this ex parte reexamination proceeding should be directed as follows:

By **U.S. Postal Service Mail** to:

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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